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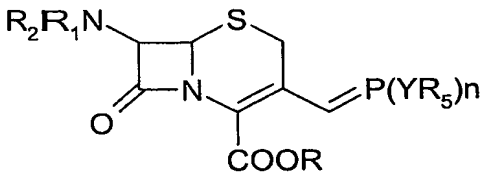
(54) Title: INTERMEDIATES USEFUL IN THE SYNTHESIS OF 3-(2-SUBSTITUTED VINYL) CEPHALOSPORINS



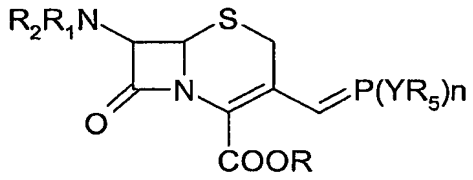
(I)

(57) Abstract: The present invention relates to crystalline intermediates useful in the synthesis of 3-(2-substituted vinyl) cephalosporins and processes for their preparation. In particular, the present invention relates to crystalline ylides of Formula I, processes for their preparation, and their use as an intermediate in thepreparation of 3-(2-substituted vinyl) cephalosporins.

INTERMEDIATES USEFUL IN THE SYNTHESIS OF 3-(2-SUBSTITUTED VINYL) CEPHALOSPORINS

Field of the Invention

The present invention relates to crystalline intermediates useful in the synthesis of 3-(2-substituted vinyl) cephalosporins and processes for their preparation. In particular, the present invention relates to crystalline ylides of Formula I, processes for their preparation, and their use as an intermediate in the preparation of 3-(2-substituted vinyl) cephalosporins.



FORMULA I

Background of the Invention

Cephalosporin antibiotics belonging to the class of 3-(2-substituted vinyl) cephalosporins have a very broad spectrum of antimicrobial activity. Cefditoren pivoxil, which belongs to this class, is highly active not only against a variety of gram-positive and gram-negative bacteria but also against some resistant strains of bacteria (see, e.g., European Patent No. 175,610).

European Patent No. 175,610 describes a process for preparing Cefditoren and its pharmaceutically acceptable salts and esters. The process described is non-selective and gives more than 20% of the unwanted E-isomer, which is then separated by means of column chromatography. The yield of cefditoren or its sodium salt or its pivaloxymethyl ester is reported to be very low.

U.S. Patent No. 6,288,223 describes a process for the selective preparation of the Z-isomer of 3-2 (substituted vinyl) cephalosporins. In this process, reaction conditions as well as solvent system are selected in such a manner that during formation of the vinyl group, selectively the Z-isomer is obtained without formation of E-isomer. The process, however, still generates about 4 to 5% of unwanted E-isomer, which needs to be separated in order to get the desired purity of the finished product. The process uses lower

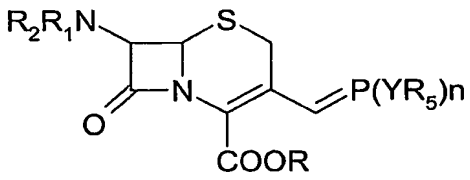
temperature of about –50 to 5°C when the vinyl group is formed by reaction between an ylide and an aldehyde. Stringent conditions are adopted for deprotection of the protected amino and carboxyl functionalities. The process isolates every intermediate followed by its purification and therefore is very time consuming. It gives a reduced yield of Cefditoren pivoxil.

U.S. Patent No. 5,616,703 describes a process for separating cephalosporin isomers by forming amine salts. The process described therein produces the intermediates in which the unwanted E isomer is more than 20%, which is then depleted by forming amine salts. In this process the yield of the intermediate is reduced and the unwanted E-isomer, after separation, is removed from the process.

Our pending PCT patent application WO 2005/016936 describes a process for selective preparation of Z-isomer of cefditoren or pharmaceutically acceptable salts and esters thereof. The process selectively prepares Z-isomer of cefditoren pivoxil having less than 1% of the E-isomer.

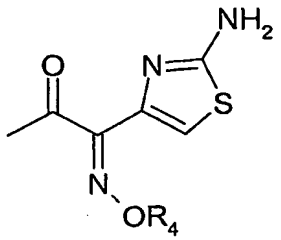
Summary of the Invention

The present inventors have surprisingly found that while preparing cefditoren pivoxil by processes described in co-pending PCT patent application WO 2005/016936, they are able to modify the reaction conditions and isolate as a crystalline solid the ylide of Formula I.



FORMULA I

In Formula I, R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt. R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally a substituted amino acid residue or a group of Formula A.



FORMULA A

In Formula A, R_4 is an optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4, and R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl.

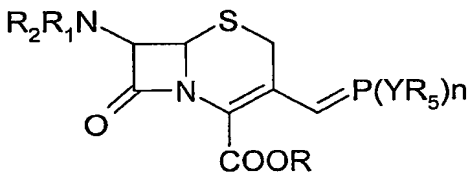
This crystalline solid of Formula I, when used as an intermediate in the synthesis of cefditoren pivoxil, can lead to a significant reduction in the consumption of 4-methylthiazole-5-carboxaldehyde of Formula II.

R_3CHO

FORMULA II

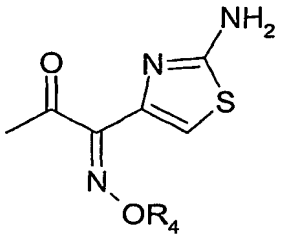
In Formula II, R_3 is 4-methylthiazole-5-yl, which is also an intermediate. This may advantageously result in significant improvement of process economics as some of the prior art processes reported use of about 6 to 25 moles of 4-methylthiazole-5-carboxaldehyde per mole of the ylide of Formula I. The present inventors have found that this consumption can be reduced to 1.0 to 2.0 moles of 4-methylthiazole-5-carboxaldehyde per mole of ylide of Formula I when the ylide is isolated from the reaction mixture as a crystalline solid.

Thus, in one general aspect there is provided a crystalline ylide of Formula I:



FORMULA I

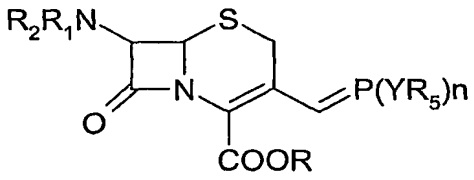
In Formula I, R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt, and R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A, n is an integer 2, 3 or 4, and R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl.



FORMULA A

In Formula A, R_4 is an optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and Y is absent or oxygen or sulphur.

In another general aspect there is provided a crystalline ylide of Formula I.

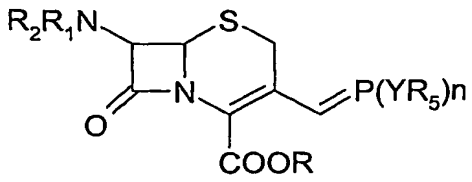


FORMULA I

In Formula I, R is diphenylmethyl, one of the R_1 and R_2 is hydrogen and other is phenylacetamido group, Y is absent, R_5 is phenyl, and n is an integer having a value of 3.

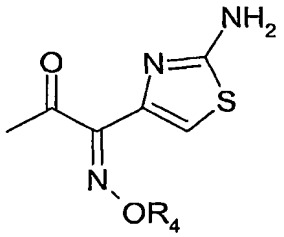
Embodiments of the crystalline ylide may include a powdered X-Ray Diffraction pattern depicted in Figure I.

In another general aspect there is provided a process for the preparation of a crystalline ylide of Formula I.



FORMULA I

In Formula I, R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt, and R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A, n is an integer 2, 3 or 4, and R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl.

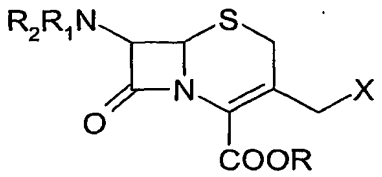


FORMULA A

In Formula A, R_4 is an optionally substituted lower alkyl wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and Y is absent or oxygen or sulphur.

The process includes the steps of

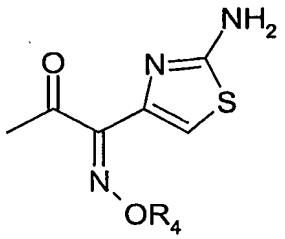
a) treating a compound of Formula III



FORMULA III

wherein,

R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt, X is chloro or bromo, and R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A,



FORMULA A

wherein R_4 is an optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, and heterocyclic containing one or more heteroatoms or halo,

with a compound of Formula IV,

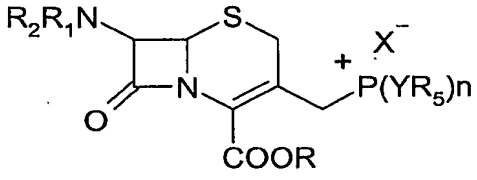
$$P(YR_5)n$$

FORMULA IV

wherein,

Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4 and R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl;

b) optionally isolating the product of Formula V,



FORMULA V

wherein R, R_1, R_2, Y, R_5, X and n are as defined above;

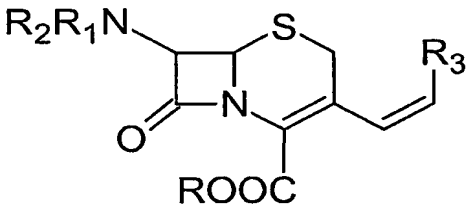
c) treating the product of step a) or b) with a base; and

d) isolating the crystalline ylide of Formula I from the reaction mass.

Embodiments of the process may include one or more of the following features. For example, the compound of Formula IV may be selected from trimethylphosphine, triethylphosphine, tributylphosphine, triphenylphosphine, triethyl phosphite, triphenylphosphite, triethylorthophosphite or triphenylorthophosphite.

The base may be selected from an inorganic or an organic base. The base may be selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, aluminium hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium methoxide, potassium t-butoxide, sodium ethoxide, triethylamine, dicyclohexylamine or diphenylamine.

In another general aspect there is provided a process for the preparation of a compound of Formula VI.



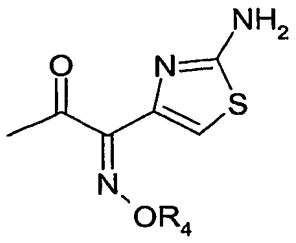
FORMULA VI

wherein,

R is hydrogen, esterified residue or a metal cation capable of forming a salt,

R_3 is hydrogen, halo, substituted C_{1-8} alkyl, aryl, aralkyl, substituted heterocyclic residue containing one or more heteroatoms selected from nitrogen, oxygen, sulphur; or SR_6 wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl, or a heterocyclic residue,

R_1 and R_2 are independently selected from hydrogen, amino protecting group or combine together to form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A,

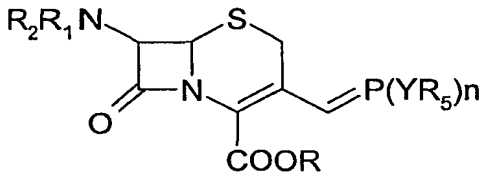


FORMULA A

wherein R_4 is an optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo,

wherein the process includes the steps of

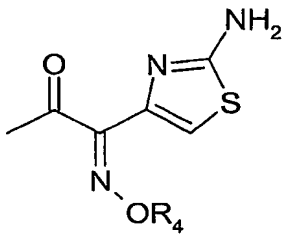
a) reacting the crystalline ylide of Formula I,



FORMULA I

wherein,

R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt, R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A, n is an integer 2, 3 or 4, and R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl,



FORMULA A

wherein R_4 is an optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and Y is absent or oxygen or sulphur,

with a compound of Formula II or a suitable chemical equivalent thereof in an organic solvent at a temperature of about –50 to 35°C,

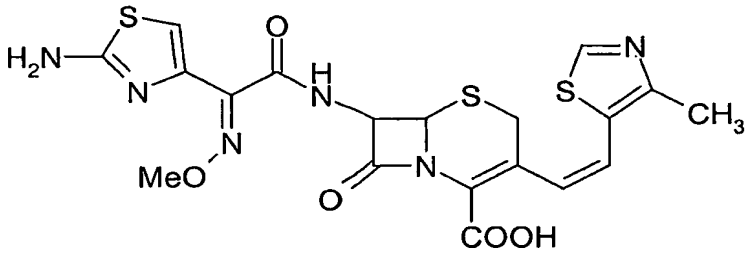
R_3CHO

FORMULA II

wherein R_3 is hydrogen, halo, substituted C_{1-8} alkyl, aryl, aralkyl, substituted heterocyclic residue containing one or more heteroatoms selected from nitrogen, oxygen, sulphur; or SR_6 wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl or a heterocyclic residue; and

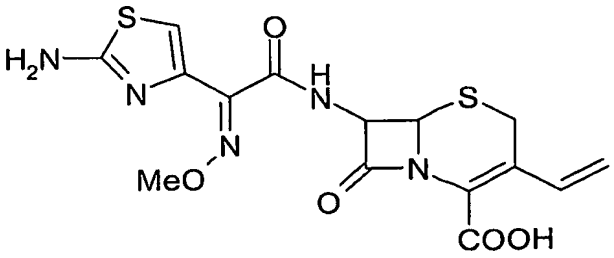
b) isolating the compound of Formula VI from the reaction mass.

In another general aspect there is provided a process that includes using the crystalline ylides above for the preparation of 3-(2-substituted vinyl) cephalosporin. Embodiments of the process may include one or more of the following features. For example, the 3-(2-substituted vinyl) cephalosporin may be cefditoren of Formula VII or pharmaceutically acceptable salts and esters thereof.



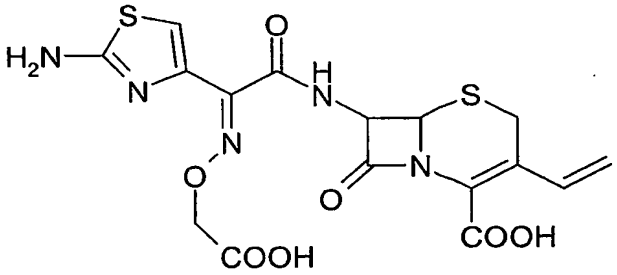
FORMULA VII

The 3-(2-substituted vinyl) cephalosporin may be cefdinir of Formula VIII or pharmaceutically acceptable salts and esters thereof.



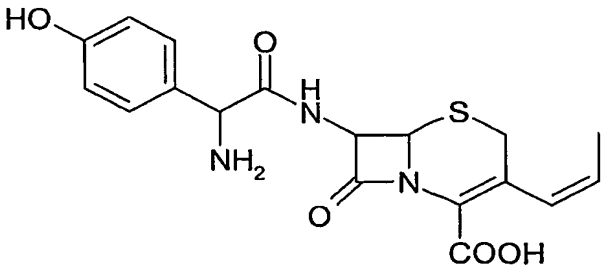
FORMULA VIII

The 3-(2-substituted vinyl) cephalosporin may be cefixime of Formula IX or pharmaceutically acceptable salts and esters thereof.



FORMULA IX

The 3-(2-substituted vinyl) cephalosporin may be cefprozil of Formula X or pharmaceutically acceptable salts and esters thereof.



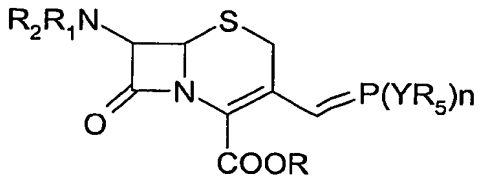
FORMULA X

Brief Description of the Drawings

Figure 1 is a powdered X-Ray Diffraction pattern of a crystalline ylide.

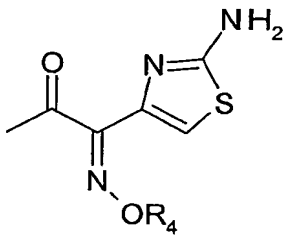
Detailed Description of the Invention

A first aspect of the present invention provides crystalline ylides of Formula I.



FORMULA I

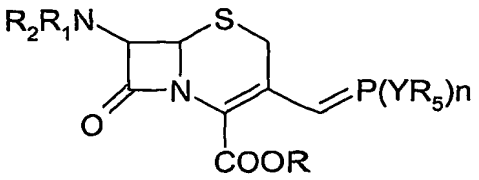
In Formula I, R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt. R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A.



FORMULA A

In Formula A, R_4 is an optionally substituted lower alkyl wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4, and R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl.

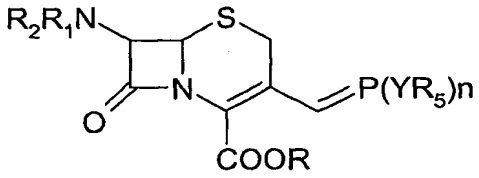
A second aspect of the present invention provides a crystalline ylide of Formula I.



FORMULA I

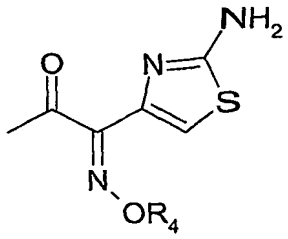
In Formula I, R is diphenylmethyl and one of the R_1 and R_2 is hydrogen and the other is a phenylacetamido group; Y is absent; R_5 is phenyl and n is integer having value 3 (herein onwards referred to as GCLH-ylide) having a powder X-Ray Diffraction pattern depicted in Figure I as shown in the accompanied drawings.

A third aspect of the present invention provides a process for preparation of crystalline ylides of Formula I.



FORMULA I

In Formula I, R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt and R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A.

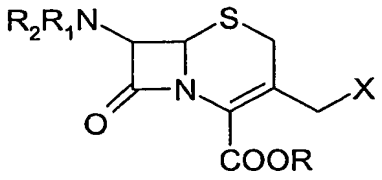


FORMULA A

In Formula A, R_4 is an optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4, and R_5

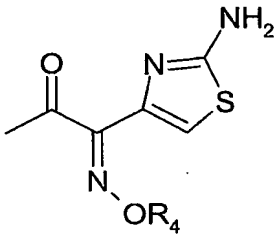
is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl. The process includes the steps of

a) treating a compound of Formula III



FORMULA III

wherein R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt; X is chloro or bromo; and R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A,



FORMULA A

wherein R_4 is a optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo,

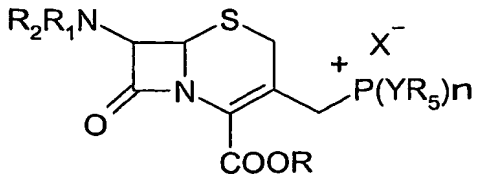
with a compound of Formula IV,

$$P(YR_5)n$$

FORMULA IV

wherein Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4, and R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl;

b) optionally isolating the product of Formula V,



FORMULA V

wherein R, R_1, R_2, Y, R_5, X and n are as defined above;

c) treating the product of step a) or b) with a base; and

d) isolating the crystalline ylide of Formula I from the reaction mass.

The compound or compounds of Formula III are treated with alkali or alkaline earth metal iodide or bromide and a phosphorous containing compound of Formula III in an organic solvent at a temperature of -10 to 50°C.

The alkali or alkaline earth metal iodide or bromide can be selected from sodium iodide, potassium iodide, sodium bromide, potassium bromide and such similar metal iodides or bromides.

The compound of Formula IV, wherein Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4, and R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl, can be selected from trimethylphosphine, triethylphosphine, tributylphosphine, triphenylphosphine, triethyl phosphite, triphenylphosphite, triethylorthophosphite or triphenylorthophosphite.

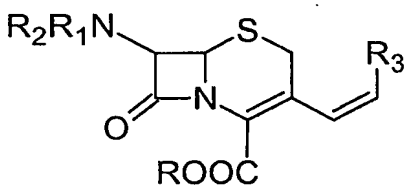
The organic solvent can be one or more of chlorinated hydrocarbons such as methylene chloride, chloroform, ethylene chloride or ethylene bromide; polar aprotic solvents such as dimethylformamide, dimethylacetamide or dimethylsulphoxide; ethers such as tetrahydrofuran, diisopropyl ether, 1,4-dioxane or diethyl ether; ketones such as acetone, methyl isobutyl ketone, methyl ethyl ketone; esters such as ethyl acetate, methyl acetate, ethyl formate, methyl formate, isopropyl acetate, n-butyl acetate, isobutyl acetate and n-propyl acetate; and lower alcohols such as methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof.

After completion of the reaction, the compound or compounds of Formula V can be isolated from the reaction mass by suitable aqueous workup, however, the reaction

mass can, as such, be taken in the next step. The reaction mass is treated with a base at a temperature between -20 to 50°C. It is also possible to cool the organic layer obtained in step a) to -5 to 25°C and slowly add a solution of base in water or suitable organic solvent over a period of 15 minutes to 1 hour by maintaining the temperature. Ylides of Formula I start separating out from the reaction mass as a crystalline solid. After complete precipitation of the crystalline product it is filtered and optionally dried under vacuum to get an almost quantitative yield.

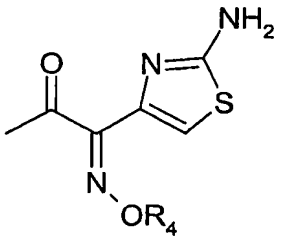
The base used in this step can be an inorganic compound such as sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, aluminium hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate; one or more organic salts such as sodium methoxide, potassium t-butoxide, sodium ethoxide; or organic ammonium compounds such as triethylamine, dicyclohexylamine or diphenylamine. For the practical utility a solution of base can be made in a suitable solvent such as water.

A fourth aspect of the present invention provides a process for the preparation of compound of Formula VI,



FORMULA VI

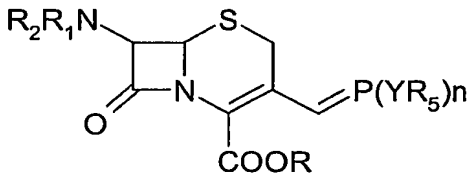
wherein R is hydrogen, esterified residue or a metal cation capable of forming a salt; R_3 is hydrogen, halo, substituted C_{1-8} alkyl, aryl, aralkyl, substituted heterocyclic residue containing one or more heteroatoms selected from nitrogen, oxygen, sulphur; or SR_6 wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl, or a heterocyclic residue; and R_1 and R_2 are independently selected from hydrogen, amino protecting group or combine together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A,



FORMULA A

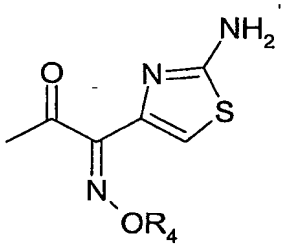
wherein R_4 is an optionally substituted lower alkyl wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo. The process includes the steps of

a) reacting the crystalline ylide of Formula I,



FORMULA I

wherein, R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt and R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A,



FORMULA A

wherein R_4 is an optionally substituted lower alkyl wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4,

and R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl,

with a compound of Formula II or a suitable chemical equivalent thereof,

R_3CHO

FORMULA II

wherein R_3 is hydrogen, halo, substituted C_{1-8} alkyl, aryl, aralkyl, substituted heterocyclic residue containing one or more heteroatoms selected from nitrogen, oxygen, sulphur; or SR_6 wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl or a heterocyclic residue in an organic solvent at a temperature of about –50 to 35°C; and

b) isolating the compound of Formula VI from the reaction mass.

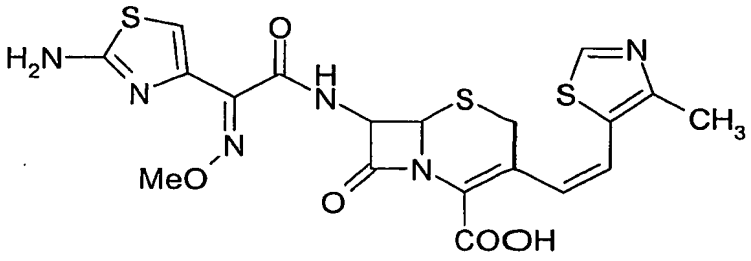
The compound of Formula I is treated with a compound of Formula II or a suitable chemical equivalent thereof, wherein R_3 is as defined above, in the presence of an organic solvent at a temperature of about –50 to 35°C. The suitable chemical equivalents include orthoesters, orthoformates, and polymeric forms of compound of Formula II. After completion of the reaction, it is quenched by addition of water followed by washing of the organic layer with sodium bisulphite solution to eliminate aldehydic and related impurities generated during reaction. The compound of Formula VI can then be isolated from the organic layer by suitable methods of isolation, which include evaporation of the organic solvent to get the product, precipitation of the product from the organic solvent by addition of anti-solvent, and the like.

The organic solvent can be one or more of chlorinated hydrocarbons such as chloroform or methylene chloride; lower alkanols such as methanol, ethanol, n-propanol, isopropanol and n-butanol; ethers such as tetrahydrofuran, diethyl ether, 1,4-dioxane; esters such as ethyl acetate, n-butyl acetate, isopropyl acetate, etc.; or ketones such as acetone, ethyl methyl ketone or mixtures thereof. A chlorinated hydrocarbon containing a lower alkanol is a preferred solvent mixture.

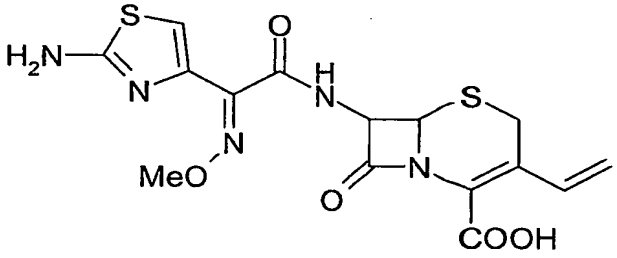
A fifth aspect of the present invention provides use of crystalline ylides of Formula I as intermediates in the synthesis of 3-(2-substituted vinyl) cephalosporin commercially

used as antimicrobials for the treatment of infectious diseases caused by gram positive, gram negative, and resistant strains of bacteria.

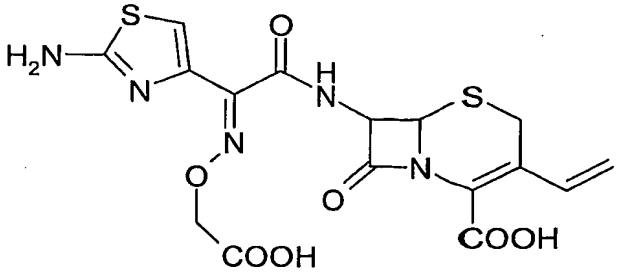
Examples of 3-(2-substituted vinyl) cephalosporins include cefditoren of Formula VII, cefdinir of Formula VIII, cefixime of Formula IX, cefprozil of Formula X or pharmaceutically acceptable salts and esters thereof.



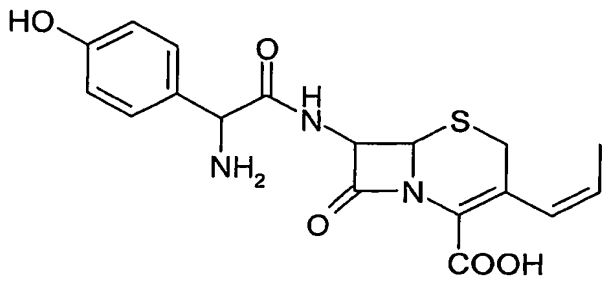
FORMULA VII



FORMULA VIII



FORMULA IX



FORMULA X

While the present inventions have been described in terms of their specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present inventions.

EXAMPLES

Example 1: Preparation of 1,1-diphenylmethyl 7-(phenylacetamido)-3-[(triphenylphoshoranylidene)methyl]-3-cepheme-4-carboxylate

To a stirred mixture of dimethylformamide (20 ml) and methylene chloride (10 ml) at ambient temperature was added 4-diphenylmethyl 7-phenylacetamido-3-chloromethyl-3-cephem-4-carboxylate (10 g) followed by addition of triphenylphosphine (0.51 g) and sodium bromide (0.23 g). This mixture was stirred for 2 to 3 hours and cooled to 10 to 15°C, followed by addition of sodium carbonate (16 ml, 10% aqueous solution). The temperature was raised to 20 to 25°C and stirring was continued for 1.5 hours. The title compound was filtered as crystalline solid (16 g) under suction.

Example 2: Preparation of Cefditoren Acid Sodium Salt

Step A) Preparation of 7-Amino-3-[2-(4-Methylthiazol-5-Yl)Vinyl]-3-Cepheme-4-Carboxylic Acid

1,1-diphenylmethyl 7-(phenylacetamido)-3-[(triphenylphoshoranylidene)methyl]-3-cephem-4-carboxylate (16 g) was mixed with methylene chloride (120 ml) and 1-propanol (40 ml) followed by addition of 4-methylthiazol-5-carboxaldehyde (3 g). The resultant heterogeneous mixture was stirred at 20 to 25°C for 20 to 22 hours. Progress of the reaction was monitored by HPLC. After completion, the reaction mixture was sequentially washed with 3% sodium bisulfite (100 ml) and water (100 ml). The organic layer was concentrated under reduced pressure to get an oily residue of 1,1,-

diphenylmethyl 7-(phenylacetamido)-3-[2-(4-methylthiazol-5-yl)vinyl]-3-cepheme-4-carboxylate. To this oily residue phenol (60 ml) was added to the residue to get a clear solution. This solution was stirred at 40 to 50°C for 10 to 12 hours and n-butyl acetate (150 ml) was added to the reaction mass followed by cooling to 5 to 10°C. The organic portion was extracted with sodium bicarbonate solution (0.17 Molar, 2 x 150 ml). The aqueous layer was washed with n-butyl acetate (2 x 150 ml) to remove traces of phenol. To the clear aqueous layer was added Pen-G amidase (8 g wet) at 20 to 25°C. The pH of the reaction was intermittently adjusted to 7.5 to 7.7 by slow addition of 5% sodium carbonate solution. After completion of the reaction, the enzyme was filtered and washed with de-ionized water. The filtrate was treated with activated carbon and then filtered at 30–35°C. The filtrate was cooled to 20–25°C and to it was added dilute HCl (2 Molar) to adjust the pH to 3.0 to 3.5 in order to effect complete precipitation of the title compound. The product was filtered and sequentially washed with water and acetone and finally dried under vacuum to get 5.5 g of off-white title compound.

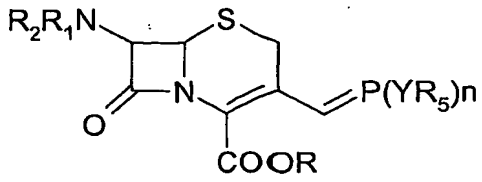
Step B) Preparation of cefditoren acid sodium salt

A suspension of product obtained in Step A) (5.0 g, 15.4 mmol) and 2-methoxyimino-2-(2-amino thiazol-4-yl)acetic acid, S-2-benzothiazole ester (6.7 g, 18.6 mmol) in aqueous tetrahydrofuran (60 ml) was stirred at 0 to 5°C. Triethylamine (2.3 ml) was added slowly at 0–5°C over 15 to 20 minutes. The mixture was stirred at 0–5°C for 2–3 hours. The reaction was quenched by addition of dichloromethane followed by layer separation. The aqueous layer was diluted with acetone to 50 ml. Sodium 2-ethylhexanoate (3.3 g, 19.8 mmol) was added to the aqueous acetone solution at 20–25°C. After stirring the mixture for sufficient time for crystallization of sodium salt of Cefditoren, acetone (50 ml) was slowly added to the reaction mass in order to complete the crystallization. The crystallized product was filtered under suction and washed with acetone (2 x 10 ml). The product was vacuum dried to get 6.5 g of off-white title compound (Yield = 75%).

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

We claim:

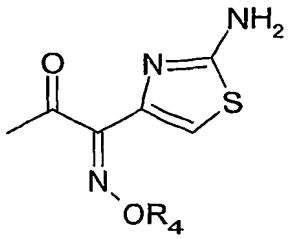
1. A crystalline ylide of Formula I,



FORMULA I

wherein,

R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt, and R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A,



FORMULA A

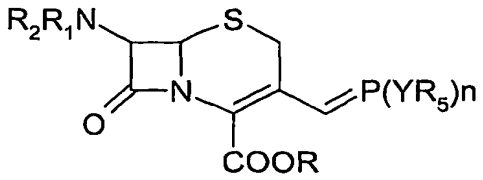
wherein,

R_4 is an optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and Y is absent or oxygen or sulphur,

n is an integer 2, 3 or 4, and

R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl.

2. A crystalline ylide of Formula I,



FORMULA I

wherein,

R is diphenylmethyl,

one of the R_1 and R_2 is hydrogen and other is phenylacetamido group,

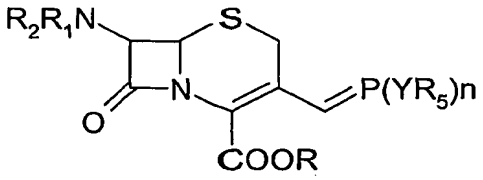
Y is absent,

R_5 is phenyl, and

n is an integer having a value of 3.

3. The crystalline ylide of claim 2 having a powdered X-Ray Diffraction pattern depicted in Figure I.

4. A process for the preparation of a crystalline ylide of Formula I,

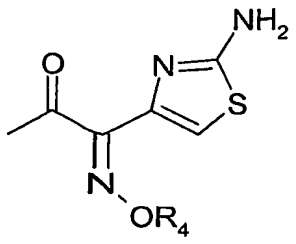


FORMULA I

wherein,

R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt, and

R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A,



FORMULA A

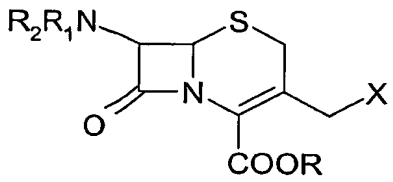
wherein R_4 is an optionally substituted lower alkyl wherein the substituents groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and Y is absent or oxygen or sulphur,

n is an integer 2, 3 or 4, and

R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl,

wherein the process comprises the steps of

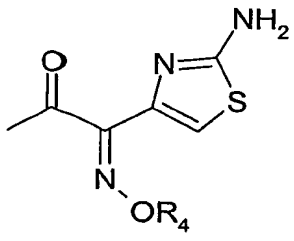
a) treating a compound of Formula III



FORMULA III

wherein,

R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt, X is chloro or bromo, and R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A,



FORMULA A

wherein R_4 is an optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, and heterocyclic containing one or more heteroatoms or halo,

with a compound of Formula IV,

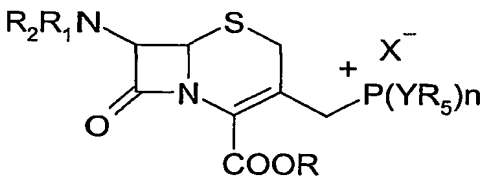
$P(YR_5)n$

FORMULA IV

wherein,

Y is absent or oxygen or sulphur, n is an integer 2, 3 or 4 and R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl;

b) optionally isolating the product of Formula V,



FORMULA V

wherein R, R_1, R_2, Y, R_5, X and n are as defined above;

c) treating the product of step a) or b) with a base; and

d) isolating the crystalline ylide of Formula I from the reaction mass.

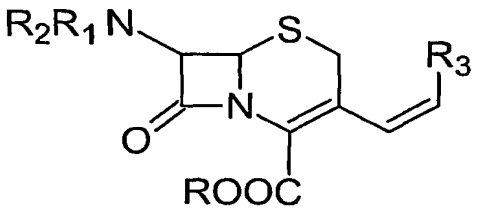
5. The process of claim 4 wherein the compound of Formula IV is selected from trimethylphosphine, triethylphosphine, tributylphosphine, triphenylphosphine, triethyl phosphite, triphenylphosphite, triethylorthophosphite or triphenylorthophosphite.

6. The process of claim 4 wherein the base is selected from an inorganic or an organic base.

7. The process of claim 6 wherein base is selected from sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, aluminium hydroxide, sodium

hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium methoxide, potassium t-butoxide, sodium ethoxide, triethylamine, dicyclohexylamine or diphenylamine.

8. A process for the preparation of a compound of Formula VI,



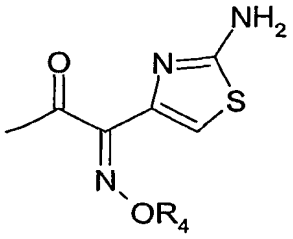
FORMULA VI

wherein,

R is hydrogen, esterified residue or a metal cation capable of forming a salt,

R_3 is hydrogen, halo, substituted C_{1-8} alkyl, aryl, aralkyl, substituted heterocyclic residue containing one or more heteroatoms selected from nitrogen, oxygen, sulphur; or SR_6 wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl, or a heterocyclic residue,

R_1 and R_2 are independently selected from hydrogen, amino protecting group or combine together to form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A,

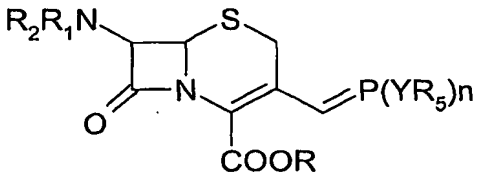


FORMULA A

wherein R_4 is an optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo,

wherein the process comprises the steps of

a) reacting the crystalline ylide of Formula I,

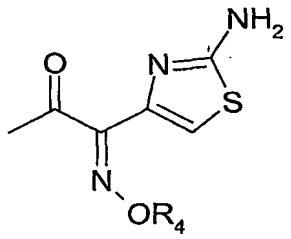


FORMULA I

wherein,

R is a hydrogen atom, esterifying residue or a metal cation capable of forming a salt,

R_1 and R_2 are independently hydrogen, monovalent amino protecting group or together form a divalent amino protecting group, optionally substituted amino acid residue or a group of Formula A,



FORMULA A

wherein R_4 is an optionally substituted lower alkyl wherein the substituent groups are selected from carboxyl, hydroxy, aryl, heterocyclic containing one or more heteroatoms or halo and Y is absent or oxygen or sulphur,

n is an integer 2, 3 or 4, and

R_5 is selected from C_1 to C_7 straight or branch chain alkyl, alkenyl, alkynyl or C_6 to C_{10} cycloalkyl, aryl or aralkyl,

with a compound of Formula II or a suitable chemical equivalent thereof in an organic solvent at a temperature of about –50 to 35°C,

R_3CHO

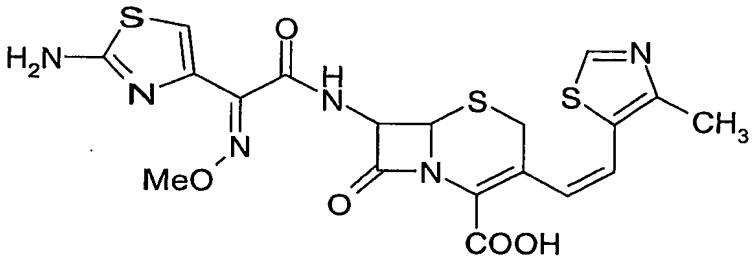
FORMULA II

wherein R_3 is hydrogen, halo, substituted C_{1-8} alkyl, aryl, aralkyl, substituted, heterocyclic residue containing one or more heteroatoms selected from nitrogen, oxygen, sulphur; or SR_6 wherein R_6 is straight or branched chain C_{1-4} alkyl, C_{1-3} alkenyl, aryl, aralkyl, substituted aralkyl or a heterocyclic residue; and

b) isolating the compound of Formula VI from the reaction mass.

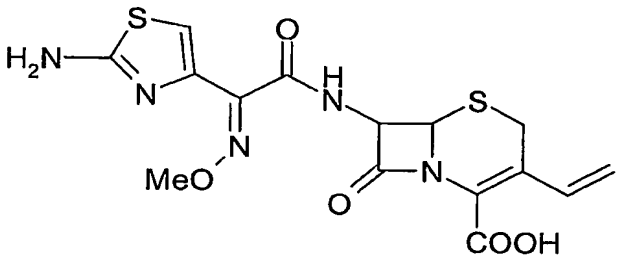
9. A process comprising using the crystalline ylide of claims 1 or 2 for the preparation of 3-(2-substituted vinyl) cephalosporin.

10. The process according to claim 9 wherein the 3-(2-substituted vinyl) cephalosporin is cefditoren of Formula VII or pharmaceutically acceptable salts and esters thereof.



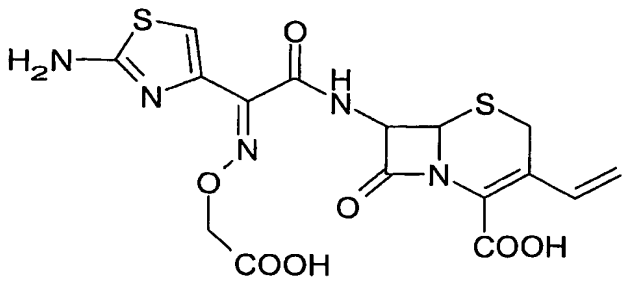
FORMULA VII

11. The process according to claim 9 wherein the 3-(2-substituted vinyl) cephalosporin is cefdinir of Formula VIII or pharmaceutically acceptable salts and esters thereof.



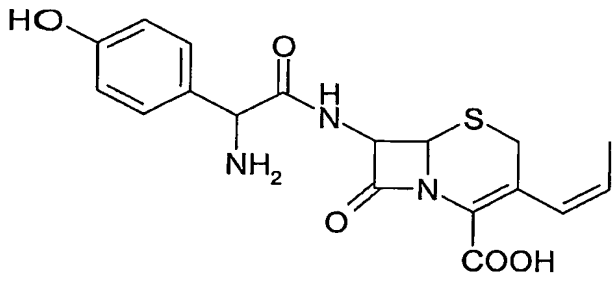
FORMULA VIII

12. The process according to claim 9 wherein the 3-(2-substituted vinyl) cephalosporin is cefixime of Formula IX or pharmaceutically acceptable salts and esters thereof.



FORMULA IX

13. The process according to claim 9 wherein the 3-(2-substituted vinyl) cephalosporin is cefprozil of Formula X or pharmaceutically acceptable salts and esters thereof.



FORMULA X

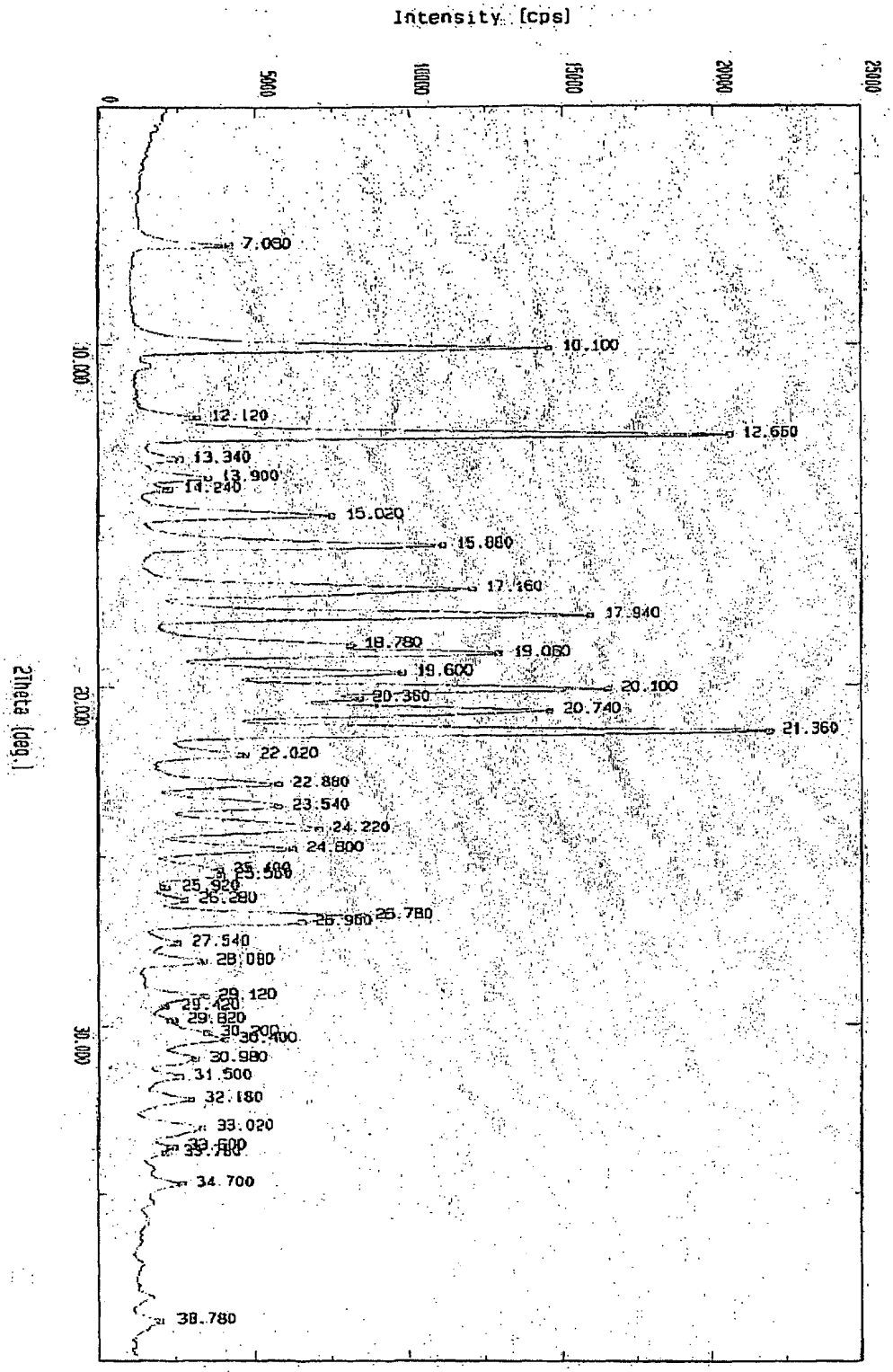


FIGURE 1: XRD OF CRYSTALLINE GCLH-YLIDE

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/IB2005/000978

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D501/00 A61K31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/083692 A (HANMI PHARM. CO., LTD; LEE, GWAN SUN; CHANG, YOUNG KIL; KIM, HONG SUN;) 24 October 2002 (2002-10-24) examples	1,2
X	EP 1 016 665 A (MEIJI SEIKA KAISHA, LTD) 5 July 2000 (2000-07-05) page 10 - page 11; examples	1,2

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
23 June 2005	30/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Menegaki, F

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INTERNATIONAL SEARCH REPORT

Interna[illegible] Application No
PCT/IB2005/000978

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	EP 0 175 610 A (MEIJI SEIKA KAISHA LTD; MITSUHASHI, SUSUMU) 26 March 1986 (1986-03-26) cited in the application examples	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

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